



COPY

SEQUENCE LISTING

<110> BAM, NARENDRA
BONGERS, JACOB
KIRKPATRICK, ROBERT B.
JANSON, CHERYL A.
JOHANSON, KYUNG
QIU, XIANYANG
YEH, PING

<120> CONJUGATES COMPRISING HUMAN IL-18 AND
SUBSTITUTION MUTANTS THEREOF

<130> PU60053

<140> 10/823,964

<141> 2004-04-14

<150> 60/462,947

<151> 2003-04-15

<160> 28

<170> FastSEQ for Windows Version 4.0

<210> 1

<211> 157

<212> PRT

<213> Homo sapiens

<400> 1

Tyr	Phe	Gly	Lys	Leu	Glu	Ser	Lys	Leu	Ser	Val	Ile	Arg	Asn	Leu	Asn
1				5					10					15	
Asp	Gln	Val	Leu	Phe	Ile	Asp	Gln	Gly	Asn	Arg	Pro	Leu	Phe	Glu	Asp
		20					25					30			
Met	Thr	Asp	Ser	Asp	Cys	Arg	Asp	Asn	Ala	Pro	Arg	Thr	Ile	Phe	Ile
		35				40						45			
Ile	Ser	Met	Tyr	Lys	Asp	Ser	Gln	Pro	Arg	Gly	Met	Ala	Val	Thr	Ile
	50				55					60					
Ser	Val	Lys	Cys	Glu	Lys	Ile	Ser	Thr	Leu	Ser	Cys	Glu	Asn	Lys	Ile
65				70					75					80	
Ile	Ser	Phe	Lys	Glu	Met	Asn	Pro	Pro	Asp	Asn	Ile	Lys	Asp	Thr	Lys
		85						90						95	
Ser	Asp	Ile	Ile	Phe	Phe	Gln	Arg	Ser	Val	Pro	Gly	His	Asp	Asn	Lys
		100						105					110		
Met	Gln	Phe	Glu	Ser	Ser	Ser	Tyr	Glu	Gly	Tyr	Phe	Leu	Ala	Cys	Glu
		115					120					125			
Lys	Glu	Arg	Asp	Leu	Phe	Lys	Leu	Ile	Leu	Lys	Lys	Glu	Asp	Glu	Leu
	130					135					140				
Gly	Asp	Arg	Ser	Ile	Met	Phe	Thr	Val	Gln	Asn	Glu	Asp			
145				150						155					

<210> 2

<211> 157

<212> PRT

<213> Mus musculus

<400> 2

```
Asn Phe Gly Arg Leu His Cys Thr Thr Ala Val Ile Arg Asn Ile Asn
 1          5          10          15
Asp Gln Val Leu Phe Val Asp Lys Arg Gln Pro Val Phe Glu Asp Met
          20          25          30
Thr Asp Ile Asp Gln Ser Ala Ser Glu Pro Gln Thr Arg Leu Ile Ile
          35          40          45
Tyr Met Tyr Lys Asp Ser Glu Val Arg Gly Leu Ala Val Thr Leu Ser
          50          55          60
Val Lys Asp Ser Lys Met Ser Thr Leu Ser Cys Lys Asn Lys Ile Ile
          65          70          75          80
Ser Phe Glu Glu Met Asp Pro Pro Glu Asn Ile Asp Asp Ile Gln Ser
          85          90          95
Asp Leu Ile Phe Phe Gln Lys Arg Val Pro Gly His Asn Lys Met Glu
          100          105          110
Phe Glu Ser Ser Leu Tyr Glu Gly His Phe Leu Ala Cys Gln Lys Glu
          115          120          125
Asp Asp Ala Phe Lys Leu Ile Leu Lys Lys Lys Asp Glu Asn Gly Asp
          130          135          140
Lys Ser Val Met Phe Thr Leu Thr Asn Leu His Gln Ser
          145          150          155
```

<210> 3

<211> 203

<212> PRT

<213> Homo sapiens

<400> 3

```
Met His His His His His His Thr Arg Gly Met Ala Ala Glu Pro Val
 1          5          10          15
Glu Asp Asn Cys Ile Asn Phe Val Ala Met Lys Phe Ile Asp Asn Thr
          20          25          30
Leu Tyr Phe Ile Ala Glu Asp Asp Glu Asn Leu Glu Ser Asp Tyr Phe
          35          40          45
Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn Asp Gln
          50          55          60
Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp Met Thr
          65          70          75          80
Asp Ser Asp Cys Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile Ile Ser
          85          90          95
Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile Ser Val
          100          105          110
Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile Ile Ser
          115          120          125
Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys Ser Asp
          130          135          140
Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys Met Gln
          145          150          155          160
Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu Lys Glu
          165          170          175
Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu Gly Asp
          180          185          190
```

Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
195 200

<210> 4
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<223> Whereby the Cysteine at position 38 of this human IL-18
sequence has been replaced with Serine.

<400> 4
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
1 5 10 15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
20 25 30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
35 40 45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
50 55 60
Ser Val Lys Cys Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
65 70 75 80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
85 90 95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
100 105 110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
115 120 125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu
130 135 140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
145 150 155

<210> 5
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<223> Whereby the Cysteine at position 38 of this human IL-18
sequence has been replaced with Serine, the Cysteine at
position 68 has been replaced with Aspartic acid, and the
Asparagine at position 78 has been replaced with Cysteine.

<400> 5
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
1 5 10 15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
20 25 30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
35 40 45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
50 55 60

Ser	Val	Lys	Asp	Glu	Lys	Ile	Ser	Thr	Leu	Ser	Cys	Glu	Cys	Lys	Ile
65					70					75					80
Ile	Ser	Phe	Lys	Glu	Met	Asn	Pro	Pro	Asp	Asn	Ile	Lys	Asp	Thr	Lys
			85						90					95	
Ser	Asp	Ile	Ile	Phe	Phe	Gln	Arg	Ser	Val	Pro	Gly	His	Asp	Asn	Lys
		100						105					110		
Met	Gln	Phe	Glu	Ser	Ser	Ser	Tyr	Glu	Gly	Tyr	Phe	Leu	Ala	Cys	Glu
		115					120					125			
Lys	Glu	Arg	Asp	Leu	Phe	Lys	Leu	Ile	Leu	Lys	Lys	Glu	Asp	Glu	Leu
	130					135					140				
Gly	Asp	Arg	Ser	Ile	Met	Phe	Thr	Val	Gln	Asn	Glu	Asp			
145					150					155					

<210> 6
 <211> 157
 <212> PRT
 <213> Homo sapiens

<220>
 <223> Whereby the Cysteine at position 38 of thi human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Aspartic acid, and the Glutamic acid at position 121 has been replaced with Cysteine.

Tyr	Phe	Gly	Lys	Leu	Glu	Ser	Lys	Leu	Ser	Val	Ile	Arg	Asn	Leu	Asn
1				5					10					15	
Asp	Gln	Val	Leu	Phe	Ile	Asp	Gln	Gly	Asn	Arg	Pro	Leu	Phe	Glu	Asp
		20						25				30			
Met	Thr	Asp	Ser	Asp	Ser	Arg	Asp	Asn	Ala	Pro	Arg	Thr	Ile	Phe	Ile
		35					40					45			
Ile	Ser	Met	Tyr	Lys	Asp	Ser	Gln	Pro	Arg	Gly	Met	Ala	Val	Thr	Ile
	50				55					60					
Ser	Val	Lys	Asp	Glu	Lys	Ile	Ser	Thr	Leu	Ser	Cys	Glu	Asn	Lys	Ile
65					70					75					80
Ile	Ser	Phe	Lys	Glu	Met	Asn	Pro	Pro	Asp	Asn	Ile	Lys	Asp	Thr	Lys
			85						90					95	
Ser	Asp	Ile	Ile	Phe	Phe	Gln	Arg	Ser	Val	Pro	Gly	His	Asp	Asn	Lys
		100						105					110		
Met	Gln	Phe	Glu	Ser	Ser	Ser	Tyr	Cys	Gly	Tyr	Phe	Leu	Ala	Cys	Glu
		115					120					125			
Lys	Glu	Arg	Asp	Leu	Phe	Lys	Leu	Ile	Leu	Lys	Lys	Glu	Asp	Glu	Leu
	130					135					140				
Gly	Asp	Arg	Ser	Ile	Met	Phe	Thr	Val	Gln	Asn	Glu	Asp			
145					150					155					

<210> 7
 <211> 157
 <212> PRT
 <213> Homo sapeins

<220>
 <223> Whereby the Cysteine at position 38 of this human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Aspartic acid, and the Leucine at position 144

has been replaced with Cysteine.

<400> 7

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
 1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
      20           25           30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
      35           40           45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
      50           55           60
Ser Val Lys Asp Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
      65           70           75           80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
      85           90           95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
      100          105          110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
      115          120          125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Cys
      130          135          140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
      145          150          155
```

<210> 8

<211> 157

<212> PRT

<213> Homo sapiens

<220>

<223> Whereby the Cysteine at position 38 of the human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Aspartic acid, and Aspartic acid at position 157 has been replaced with Cysteine.

<400> 8

```
Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
 1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
      20           25           30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
      35           40           45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
      50           55           60
Ser Val Lys Asp Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
      65           70           75           80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
      85           90           95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
      100          105          110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
      115          120          125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Leu
      130          135          140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Cys
      145          150          155
```

<210> 9
 <211> 157
 <212> PRT
 <213> Homo sapeins

<220>

<223> Whereby the Cysteine at position 38 of the human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Serine, and Leucine at position 144 has been replaced with Cysteine.

<400> 9

```

Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
          20           25           30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
          35           40           45
Ile Ser Met Tyr Lys Asp Ser Gln Pro Arg Gly Met Ala Val Thr Ile
          50           55           60
Ser Val Lys Ser Glu Lys Ile Ser Thr Leu Ser Cys Glu Asn Lys Ile
65           70           75           80
Ile Ser Phe Lys Glu Met Asn Pro Pro Asp Asn Ile Lys Asp Thr Lys
          85           90           95
Ser Asp Ile Ile Phe Phe Gln Arg Ser Val Pro Gly His Asp Asn Lys
          100          105          110
Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
          115          120          125
Lys Glu Arg Asp Leu Phe Lys Leu Ile Leu Lys Lys Glu Asp Glu Cys
          130          135          140
Gly Asp Arg Ser Ile Met Phe Thr Val Gln Asn Glu Asp
145           150           155

```

<210> 10
 <211> 157
 <212> PRT
 <213> Homo sapiens

<220>

<223> Whereby the Cysteine at position 38 of the human IL-18 sequence has been replaced with Serine, the Cysteine at position 68 has been replaced with Serine, and Aspartic acid at position 157 has been replaced with Cysteine.

<400> 10

```

Tyr Phe Gly Lys Leu Glu Ser Lys Leu Ser Val Ile Arg Asn Leu Asn
1           5           10           15
Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu Phe Glu Asp
          20           25           30
Met Thr Asp Ser Asp Ser Arg Asp Asn Ala Pro Arg Thr Ile Phe Ile
          35           40           45

```

Ile	Ser	Met	Tyr	Lys	Asp	Ser	Gln	Pro	Arg	Gly	Met	Ala	Val	Thr	Ile
50						55					60				
Ser	Val	Lys	Ser	Glu	Lys	Ile	Ser	Thr	Leu	Ser	Cys	Glu	Asn	Lys	Ile
65					70					75					80
Ile	Ser	Phe	Lys	Glu	Met	Asn	Pro	Pro	Asp	Asn	Ile	Lys	Asp	Thr	Lys
			85						90					95	
Ser	Asp	Ile	Ile	Phe	Phe	Gln	Arg	Ser	Val	Pro	Gly	His	Asp	Asn	Lys
		100						105					110		
Met	Gln	Phe	Glu	Ser	Ser	Ser	Tyr	Glu	Gly	Tyr	Phe	Leu	Ala	Cys	Glu
		115					120					125			
Lys	Glu	Arg	Asp	Leu	Phe	Lys	Leu	Ile	Leu	Lys	Lys	Glu	Asp	Glu	Leu
	130					135					140				
Gly	Asp	Arg	Ser	Ile	Met	Phe	Thr	Val	Gln	Asn	Glu	Cys			
145					150					155					

<210> 11
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Tryptic peptides predicted for S-carboxymethylated
 wild type IL-18

<400> 11
 Tyr Phe Gly Lys
 1

<210> 12
 <211> 4
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Tryptic peptides predicted for S-carboxymethylated
 wild type IL-18

<400> 12
 Leu Glu Ser Lys
 1

<210> 13
 <211> 5
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Tryptic peptides predicted for S-carboxymethylated
 wild type IL-18

<400> 13

Leu Ser Val Ile Arg
1 5

<210> 14
<211> 26
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 14
Asn Leu Asn Asp Gln Val Leu Phe Ile Asp Gln Gly Asn Arg Pro Leu
1 5 10 15
Phe Glu Asp Met Thr Asp Ser Asp Cys Arg
20 25

<210> 15
<211> 5
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 15
Asp Asn Ala Pro Arg
1 5

<210> 16
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 16
Thr Ile Phe Ile Ile Ser Met Tyr Lys
1 5

<210> 17
<211> 5
<212> PRT
<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 17

Asp Ser Gln Pro Arg
1 5

<210> 18

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 18

Gly Met Ala Val Thr Ile Ser Val Lys
1 5

<210> 19

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 19

Ile Ser Thr Leu Ser Cys Glu Asn Lys
1 5

<210> 20

<211> 5

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 20

Ile Ile Ser Phe Lys
1 5

<210> 21

<211> 9

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 21

Glu Met Asn Pro Pro Asp Asn Ile Lys
1 5

<210> 22

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 22

Ser Asp Ile Ile Phe Phe Gln Arg
1 5

<210> 23

<211> 8

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 23

Ser Val Pro Gly His Asp Asn Lys
1 5

<210> 24

<211> 17

<212> PRT

<213> Artificial Sequence

<220>

<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 24

Met Gln Phe Glu Ser Ser Ser Tyr Glu Gly Tyr Phe Leu Ala Cys Glu
1 5 10 15
Lys

<210> 25
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 25
Asp Leu Phe Lys
1

<210> 26
<211> 4
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 26
Leu Ile Leu Lys
1

<210> 27
<211> 7
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18

<400> 27
Glu Asp Glu Leu Gly Asp Arg
1 5

<210> 28
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Tryptic peptides predicted for S-carboxymethylated
wild type IL-18